

## **REMARKS**

### **I. Preliminary Remarks and Amendments**

Claims 1-39 are currently under consideration and stand rejected. Claims 1-3, 5-6, 8-12, 32, and 34 are amended herein. Claim 40 is a new claim. Claims 4, 7, 13-31, 33, 35-39 are canceled. Thus, claims 1-3, 5-6, 8-12, 32, 34, and 40 are currently pending. Support for the addition and amendments to the claims is found throughout the specification and the original claims. Accordingly, the addition and amendments do not include new matter.

Applicants do not intend by any amendments to abandon the subject matter of any claim previously presented. Applicants reserve the right to pursue the subject matter of such claims in duly filed continuing applications, and any issues of patentability will be addressed at that time. This response is timely filed with an Extension of Time.

### **II. Patentability Arguments**

Reconsideration and withdrawal of the rejections is solicited for the reasons set out below.

#### **A. The Rejection of Claims 1-31 under 35 U.S.C. § 112, First and Second Paragraphs, May Properly Be Withdrawn.**

Claims 1-31 were rejected under 35 U.S.C. §112, first and second paragraphs, because assertedly “the claimed invention is not described, or is not described in such full, clear, and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.” Examiner states that the claim 1 process will not produce the product as specified, and alternatively, the specification does not teach how to do the process of claim 1 because XH in formula I is not produced in the final product of the process of claim 1. Examiner also states “The Bateson et al. reference, doing the N-deacylation on a virtually identical compound (differing only in the nature of the ester group at a remote point), does not directly obtain the salt.” The Applicants respectfully traverse this rejection.

Applicants have amended claims 1-3, 5-6, 8-12, 32, and 34, as shown above. In addition, Applicants have canceled claims 4, 7, 13-31, 33, 35-39. Thus the rejection of claims 4, 7, and 13-

31 under 35 U.S.C. § 112, first and second paragraphs, is rendered moot. Claims 1-3, 5-6, and 8-12 remain under consideration for this rejection.

When the process of claim 1 is followed, the product is a compound of formula I, which is the hydrochloride salt. Applicants have submitted, as part of this Request for Continued Examination, a first Declaration (hereinafter, the Declaration) from the inventor stating this. When the Bateson process was utilized, a compound of formula I was obtained. As stated in Items 8 and 9, "for the synthesis of a compound of formula I, utilizing the Bateson process, an ester compound of formula IIIc, where R<sup>1</sup> is *para*-methoxybenzyl and R<sup>2</sup> is phenyl, was converted to a compound of formula I, where R<sup>1</sup> is *para*-methoxybenzyl and X is chloro, using the four step process set out in Example 1 of the above-identified application. The form and purity of the resulting compound of formula I from the reaction was unacceptable for further use due to an unacceptable high level of impurities. The crude product required purification by column chromatography and the compound of formula I was obtained in an overall yield of 22% as a yellow foam." Likewise, when the process of claim 1 was followed, a compound of formula I was obtained. As stated in Items 10 and 11 of the Declaration, "the Bateson process was compared with the process of present claim 1 wherein the compound of formula IIIc, where R<sup>1</sup> is *para*-nitrobenzyl and R<sup>2</sup> is phenyl, to produce a compound of formula I, where R<sup>1</sup> is *para*-nitrobenzyl and X is chloro. The compound of formula I obtained by the practice of the process of claim 1 of the present application was in a crystalline solid form of sufficiently high purity so that no purification operations were necessary prior to further use. The compound of formula I was obtained in a yield of 45%."

This process is exemplified in Example 1 of the specification. Particularly, in step (d) of claim 1, the Lewis acid of structure PX<sub>5</sub> wherein X is halo provides the X for the XH portion of a compound of formula I. This is supported on page 5, lines 25-27 of the specification where it is stated "Suitable acids in said process of the invention for the conversion of compounds of formula (II) into compounds of formula (I) include Lewis Acids, such as phosphorus pentachloride or phosphorus pentabromide; preferably phosphorus pentachloride."

For all of the foregoing reasons, the Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first and second paragraphs.

**B. The Obviousness Rejection of Claims 1-4, 7-15, 25, and 28-39 under 35 U.S.C. § 103(a) May Be Properly Withdrawn.**

Claims 1-4, 7-15, 25, and 28-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bateson et al (US 6,001,997).

Applicants have amended the claims as shown above. Claim 1 is amended to incorporate claims 4 and 7. Claims 4, 7, 13-31, 33, 35-39 are canceled. As such, the rejection of claims 4, 7, 13-15, 25, 28-31, 33, 35-39 under 35 U.S.C. § 103(a) is rendered moot. Claims 1-3, 8-12, 32, and 34 remain under consideration for this rejection.

**1. Rejection of claims 1-3, 4 and 7 (which are now incorporated in amended claim 1), 8-9, 32, and 34.** The process set forth in the Bateson et al. reference (hereinafter Bateson) for the preparation of a compound of formula I differs from the process of the instant application in the values of the R<sup>1</sup> and R<sup>2</sup> substituents. In Bateson, CO<sub>2</sub>R<sup>1</sup> is an ester derivative and R<sup>2</sup>C(O) is an acyl group, while in the instant application, R<sup>1</sup> is *para*-nitrobenzyl and R<sup>2</sup> is C<sub>1-6</sub>alkyl, C<sub>6-10</sub>aryl, C<sub>6-10</sub>arylC<sub>1-6</sub>alkyl, or dithianyl. The rejection of the claims is grounded in the conclusion drawn by the Examiner that the *para*-nitrobenzyl used in the present invention as the protecting agent is obvious in view of the alleged equivalence to the groups taught by Bateson. The Examiner states "Applicants need to show that unexpected effects arise from the use of one protecting group rather than another."

The inventor states in the Declaration the unexpected results of using the process of amended claim 1. The process of claim 1 of the present application resulted in a compound of formula I in a yield of 45% and in a crystalline solid form of sufficiently high purity so that no purification operations were necessary prior to further use. (see Declaration, Item 11)

The synthesis of a compound of formula I, utilizing the Bateson process in which an ester compound of formula IIIc, where R<sup>1</sup> is *para*-methoxybenzyl and R<sup>2</sup> is phenyl, was converted to a compound of formula I, where R<sup>1</sup> is *para*-methoxybenzyl and X is chloro, using the four step process set out in Example 1 of the above-identified application, resulted in a compound of formula I with a form and purity unacceptable for further use due to an unacceptable high level of impurities. The crude product required purification by column chromatography. The

compound of formula **I** was obtained in an overall yield of 22% as a yellow foam. (See Declaration Items 8-9)

As stated in Item 12 of the Declaration, "the above results establish the clear superiority of the present process of claim 1 over the Bateson process. That the compound having the formula **I** was produced and isolated in acceptable purity and with higher yields, as set forth in Example 1 of the specification of the present application, and that it was very useful in the synthesis of cefovecin, was surprising." The Bateson process produced a yellow foamy intermediate with unacceptable contaminants that then required purification of the low-yielding intermediate. Applicants' invention produces a much higher yield of a crystalline solid form and such a low amount of contaminants that a purification step is not needed. The intermediate produced by Applicants' invention can be used directly in the next step of the process used to produce the final product.

Independent claims 1, 32, and 34 are not obvious for all of the reasons stated herein. Claims 2-3 and 8-9, which depend from claim 1, are also not obvious because they further limit the independent claim.

**2. Rejection of claims 10-12.** The process set forth in Bateson for the preparation of a compound of formula **IIIc** differs from the process of the instant application (claim 10, example 5) in the values of the  $R^1$  and  $R^2$  substituents. In Bateson,  $CO_2R^1$  is an ester derivative and  $R^2C(O)$  is an acyl group, while in the instant application,  $R^1$  is *para*-nitrobenzyl and  $R^2$  is  $C_{1-6}$ alkyl,  $C_{6-10}$ aryl,  $C_{6-10}$ aryl $C_{1-6}$ alkyl, or dithianyl. The rejection of the claims is grounded in the conclusion drawn by the Examiner that the *para*-nitrobenzyl used in the present invention as the protecting agent is obvious in view of the alleged equivalence to the groups taught by Bateson.

The inventor states in the Declaration the unexpected results of using the process of example 5 (amended claim 10). The process of claim 10 of the present application resulted in a compound of formula **IIIc** in a yield of 86% and in a solid form of sufficiently high purity so that no purification operations were necessary prior to further use. (see Declaration, Item 16)

The synthesis of a compound of formula **IIIc**, utilizing the Bateson process in which an ester compound of formula **V** where  $R^1$  is *para*-methoxybenzyl and  $R^2$  is phenyl, is treated with 2-bromo-1-(tetrahydro-furan-2-yl)-ethanone, under the process set out in Example 5 of the

above-identified application, where the compound of formula V is generated *in situ*; resulted in a compound of formula IIIc with a form and purity unacceptable for further use due to an unacceptable high level of impurities. The crude product required purification by column chromatography. The compound of formula IIIc was obtained in an overall yield of 55% as a yellow foam. (See Declaration Items 13-14)

As stated in Item 17 of the Declaration, "the above results establish the clear superiority of the present process of claim 10 over the Bateson process. That the compound having the formula IIIc was produced and isolated in acceptable form and with higher yields, as set forth in Example 5 of the specification of the present application, and that it was very useful in the synthesis of cefovecin, was surprising." The Bateson process produced a white foamy intermediate with unacceptable contaminants that then required purification of the low-yielding intermediate. Applicants' invention produces a much higher yield of a solid form and such a low amount of contaminants that a purification step is not needed. The intermediate produced by Applicants' invention can be used directly in the next step of the process used to produce the final product.

Independent claim 10 is not obvious for all of the reasons stated herein. Claims 11 and 12, which depend from claim 10, are also not obvious because they further limit the independent claim.

For all of the foregoing reasons, the Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a).

#### **C. Comments Regarding Traverse Presented in the Parent.**

**1. Unexpected improvement in terms of "better isolation and purification".** The Examiner stated that evidence of unexpected effects should have been presented in the form of a proper declaration under 35 USC 132. Applicants have submitted the Declaration with this Request for Continued Examination.

**2. Protecting group can be removed with sodium dithionite and under mild pH adjustment.** The Examiner stated that "removing protecting groups is a well understood area, a routine matter, and these are all expected differences, not unexpected ones. Applicants have submitted the Second Declaration in which it is stated that "removal of either the *para*-

methoxybenzyl (Bateson's process) or the *para*-nitrobenzyl (Applicant's process) protecting group under acidic conditions resulted in similar yields of 20-40%" (Item 10), "removal of either the *para*-methoxybenzyl (Bateson's process) or the *para*-nitrobenzyl (Applicant's process) protecting group using hydrogenation resulted in similar yields of 70-80%" (Item 11), "removal of the *para*-nitrobenzyl (Applicant's process) protecting group using sodium dithionite under very mild conditions without the use of hydrogenation conditions, which is not feasible for the *para*-methoxybenzyl (Bateson's process) protecting group, resulted in yields of 85-90%" (Item 12), and "the above results establish the clear superiority of the present process of claim 1 over the Bateson process" (Item 13).

**3. Higher yields are possible with pNB in the next step.** The Examiner stated that no proper evidence for this has been presented. Applicants have submitted the Declaration with this Request for Continued Examination as proper evidence.

### **III. Formality Remarks**

#### **A. The Objection to the Specification May Be Properly Withdrawn.**

Examiner objected to the abstract because "it states that there is a process, but gives virtually no indication of what that process consists of." Examiner suggested use of the amendment tendered in the parent application.

Applicants have replaced the abstract filed in the preliminary amendment of the instant application (mailed February 17, 2004) with an abstract based on amended claim 1 (see page 2 of this paper), which is similar in format to the abstract filed by amendment in the parent case (mailed April 1, 2003). Applicants respectfully request the objection to the specification be withdrawn.

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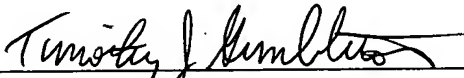
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#### **IV. Conclusions.**

In view of the amendments and remarks made herein, Applicants respectfully submit that claims 1-3, 5-6, 8-12, 32, 34, and 40 are in condition for allowance and respectfully request expedited notification of same.

Respectfully submitted,



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